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Clinical Study

Cognitive dysfunction following surgery for intracerebral glioma: influence of histopathology, lesion location, and treatment

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Summary

This study examined the relationship between cognitive function, tumor malignancy, adjunctive therapy, and lesion lateralization following surgery for intracerebral glioma. Neuropsychological test battery results showed no difference between patients with highly malignant gliomas and those with less malignant gliomas, but differences were found for tumor lateralization and type of therapy. Scores on a test of graphomotor speed were lowest for patients who had received radiation or a combination of radiation and chemotherapy, regardless of lesion location. Other test results did not differ according to type of prior treatment but were related instead to tumor lateralization. Left hemisphere lesions were associated with lower scores on verbal tests, while right hemisphere lesions were related to lower scores on a test of facial recognition.

These findings suggest that neuropsychological tests may be useful for distinguishing between the diffuse side effects of brain tumor therapy and the focal effects of tumors and surgery on brain functions. In addition, it appears that any differences in cognitive function due to tumor malignancy are eliminated or reduced following surgical intervention.

Intracerebral tumors have long been an important source of data for the study of brain-behavior relationships. Although patients with brain tumors have often served as subjects in neuropsychological research, most studies used mixed pathology samples that also included patients with other neurological conditions, such as seizure disorder or cerebrovascular accident [1]. Few studies have specifically addressed the neurobehavioral symptoms associated with intracerebral neoplasms, including the relationships between cognitive dysfunction and variables such as tumor histopathology (i.e., malignancy), form of treatment, and lesion location.

In the 1930s slowly growing brain tumors were reported to produce primarily alterations in personality or mood, while faster growing, more malignant brain tumors were found to give rise to problems with cognitive function [2]. The results of other early investigations supported the view that highly malignant neoplasms produce greater cognitive impairment [3, 4]. However, many of the patients in those studies were examined before medical intervention and they often exhibited symptoms of increased intracranial pressure, including confusion, somnolence, and papilledema. Thus, the greater cognitive impairment found in patients with malignant tumors was likely due to a higher incidence of intracranial hypertension [5].

A recent study examined a small sample of patients with tumors who had received steroids, but not surgery, for raised intracranial pressure [6]. When compared with subjects who had low-grade tumors, patients who had highly malignant tumors

performed significantly worse on tests of verbal fluency, visual memory, and visual-construction. Patients with highly malignant tumors were also reported to have severe attentional disturbances that were not found in those with less malignant lesions.

Only one large study has examined the relationship between level of malignancy and neuropsychological test performance [7]. These investigators noted worse performance on the Halstead-Reitan Neuropsychological Battery (HRNB) in patients with highly malignant tumors. However, those patients were an average of 16 years older than the patients whose tumors were less aggressive, and a correction for age was not performed. Measures on the HRNB are sensitive to age differences [8] and the failure to correct for this variable may have biased the results. Interpretation of these findings is further limited because it was not recorded whether the patients exhibited signs of raised intracranial pressure or whether they received treatment of any kind.

Effects of treatment must be considered when assessing the neurobehavioral function of brain tumor patients. Brain radiation has been reported to cause declines in cognitive function that may be progressive or have a delayed onset [9]. Treatment combining radiation with chemotherapy has been found to exacerbate impairment induced by radiation alone [10]. However, most of the prior research examining the side effects of radiation and chemotherapy has been conducted with populations other than adult patients with brain tumors, including children or patients with systemic malignancies [11, 12]. Only a few small studies have examined the cognitive side effects of therapy in adults with intracerebral glioma [9, 13]. The pattern of neuropsychological deficits in adults with glioma has been reported to be most consistent with diffuse cerebral dysfunction secondary to treatment. The location of the tumor, in contrast, has been said to be less relevant to the type and severity of cognitive impairment [14].

Research has yielded mixed findings on the relationship between tumor localization and cognitive dysfunction. One study found expected differences based on tumor lateralization, in that patients with left hemisphere tumors performed far more poorly on verbal tests than did patients with right hemisphere tumors [7]. Other investigators did not find such differences [15]. A more recent study found that patients with brain tumors had milder, less specific, and more variable deficits than those seen in patients who had cerebrovascular accidents [16].

Most evidence suggests that the relationship between brain tumor location and cognitive dysfunction is weak, that radiation and chemotherapy produce diffuse brain dysfunction, and that highly malignant tumors are associated with greater cognitive impairment. Unfortunately, all of the studies that support these conclusions either relied upon small samples or had marked problems with subject selection and confounding variables, such as the presence of acute intracranial hypertension or failure to address demographic characteristics. Thus, the need exists for a large-scale study to assess cognitive impairments associated with brain tumors and their treatment.

The present study used age-corrected test scores to examine the influence of tumor histopathology, side effects of therapy, and lesion lateralization on cognitive function in 245 patients who underwent surgery for glioma. Greater impairment was expected after adjunctive therapy (i.e., radiation, radiation plus chemotherapy) was given or in cases of glioblastoma, the most malignant form of glioma. Additionally, subjects with left hemisphere lesions were hypothesized to have lower scores on tests of verbal function, while patients with right hemisphere lesions were expected to have worse performance on tests of visuospatial skill.

Methods

Patients with a confirmed diagnosis of intracerebral glioma who underwent partial or total resection of the tumor (confirmed by computerized tomography or magnetic resonance imaging), who were medically stable, and who were more than 18 years old were included in the study. Subjects with a documented history of preexisting central nervous system disease (e.g., cerebrovascular disease, head trauma), serious psychiatric disorder, or substance abuse were excluded. The patients were also select-

ed to include only those whose tumor was unilateral and did not extend into major midline/subcortical areas (e.g., brainstem, diencephalon, third ventricle, corpus callosum). Lesion location was determined from neurosurgical and radiological reports.

Subjects were classified according to the variables shown in Table 1. All patients with the diagnosis of glioblastoma were included in one group [17], while subjects with other forms of anaplastic glioma (oligodendroglioma, ependymoma, astrocytoma, mixed glioma) were assigned to the nonglioblastoma group. Patients were also classified according to the hemisphere involved (right hemisphere, left hemisphere) and type of therapy.

All subjects in the study underwent surgery and a large percentage also received radiation therapy alone or radiation plus chemotherapy (i.e., combination therapy). Surgery and other treatments were often provided at other institutions and details about the extent of the resection, specific radiation and chemotherapy protocols, and the timing of surgery and adjunctive treatments were often unavailable. Consequently, patients were grouped according to the basic type of adjunctive therapy they had received, if any (none, radiation, combination therapy).

Demographic characteristics of the 245 patients that met the selection criteria are listed in Table 1. The mean age and years of education within this sample were 42.0 years and 14.6 years, respectively. Education did not differ significantly among the pathology, therapy, or lateralization groups. However, there was a significant difference among the therapy groups for age ($F(1, 242) = 6.24, p < 0.0023$) and, on average, patients who had not received adjunctive therapy were over five years older than those who had. This difference was likely due to referral patterns; patients who were seen for neuropsychological assessment following adjunctive treatment were often referred for further treatment after receiving their initial therapy at another institution. In contrast, patients evaluated before treatment were referred to this institution for their primary therapy and subsequently received treatment. Thus, patients who had already received radiation and/or chemotherapy were likely to be younger because they were pursuing additional treatment that might not be appropriate for older patients. Consistent with prior research, the glioblastoma patients were also significantly older than individuals with other forms of glioma ($F(1, 243) = 45.34, p < 0.0001$). There were no significant age differences between the lateralization groups.

The neuropsychological tests were administered by a neuropsychologist and by supervised technicians as part of a clinical evaluation and, in all cases, this was the initial post-surgical assessment. Measures were selected from the clinical database for the present study because they had been administered to a large proportion of the subjects and cov-

Table 1. Age and education as a function of tumor and therapy variables

Variable	n	Age		Education	
		M	SD	M	SD
Histopathology					
glioblastoma	106	47.8	11.9	14.2	3.1
nonglioblastoma	139	37.6	11.5	14.9	3.1
Therapy[a]					
none	116	45.0	13.4	14.3	3.4
radiation	51	39.7	13.1	15.1	3.0
combination[b]	78	39.1	10.5	14.4	2.9
Laterality					
left hemisphere	134	41.0	12.9	14.3	3.1
right hemisphere	111	43.3	12.4	14.9	3.2

[a] All subjects had undergone surgery

[b] Radiation plus chemotherapy.

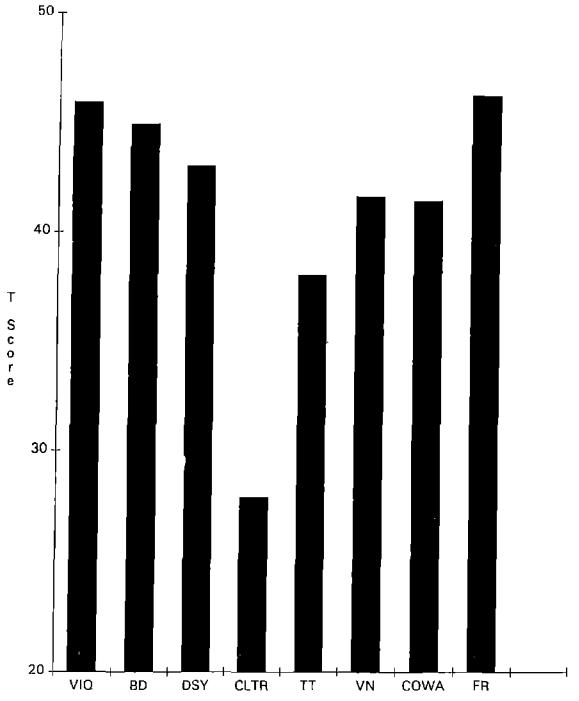

Fig. 1. T score profile for cognitive measures for the total sample of glioma patients (VIQ = Verbal IQ; BD = Block Design; DSY = Digit Symbol; CLTR = Consistent Long Term Retrieval; TT = Token Test; VN = Visual Naming Test; COWA = Controlled Oral Word Association Test; FR = Facial Recognition Test).

ered a variety of cognitive abilities. These included: verbal intelligence – Verbal IQ of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) [18]; visual-spatial organization – Block Design subtest of the WAIS-R [18]; visual motor speed – Digit Symbol subtest of the WAIS-R [18]; memory – the consistent long term retrieval (CLTR) score from the Verbal Selective Reminding test [19]; language – subtests of the Multilingual Aphasia Examination measuring naming and comprehension [20]; visual perception – Facial Recognition Test [21]; and verbal fluency – Controlled Oral World Association (COWA) [20].

Many subjects were not administered some of the tests because of time constraints in the clinic, differences in referral question, and changes in department policy during the period when these data were added to the database. Of the 245 patients, 133 had been examined with all of the neuropsychological measures and could be included in the multivariate analysis. However, the univariate analyses included the maximum number of subjects for each comparison because this increased statistical power, provided a more complete description of patients in the clinical database, and permitted examination of a sample that is more representative of adult glioma populations. In other words, subjects were not excluded from the entire study if scores were unavailable for one or more of the neuropsychological tests.

Results

Published normative data were used to correct all measures for age and, where appropriate, for gender and for education [18–21]. Scores were then converted to T scores with a mean of 50 and a standard deviation of 10 to facilitate comparability. Figure 1 presents the mean adjusted value for each of the cognitive measures. All have T scores lower than 50, which is below the expected level for normal populations

Histopathology

The influence of histopathology on cognitive function was examined through a one-way multivariate analysis of variance (MANOVA) using Pillai's criterion and using the eight neuropsychological measures as dependent variables. This analysis revealed no statistically significant differences in neuropsychological test performance between patients with glioblastoma and those in the nonglioblastoma group ($F(8, 124) = 0.76$, $p < 0.64$).

Therapy

A one-way MANOVA using Pillai's criterion indicated significant differences among therapy groups for the entire set of eight cognitive variables ($F(16, 248) = 1.74$, $p < 0.04$). Univariate analyses were completed for each neuropsychological measure and the Bonferroni inequality was used to control the Type I error rate (see Table 2) [23]. With this

statistical procedure, significant differences were obtained for the Digit Symbol subtest, and the Block Design subtest approached significance. Univariate group comparisons were then performed for the Digit Symbol subtest using Hochberg's GT2 procedure [24]. The mean score of the no-therapy group (M = 8.86, SD = 2.94) was then found to be significantly higher than the mean of the radiation (M = 7.56, SD = 2.42) or combination therapy groups (M = 6.60, SD = 2.47) ($p < 0.05$).

Lateralization

A one-way MANOVA using Pillai's criterion was used to compare the right and left hemisphere groups, and the result was highly significant ($F(8, 124) = 6.01$, $p < 0.0001$), indicating a strong relationship between overall neuropsychological test performance and hemispheric site of the tumor. Univariate analyses indicated significant differences for Verbal IQ, the Token Test, the Visual Naming Test, the COWA test, the Facial Recognition test, and the CLTR score from the verbal memory test when the Bonferroni procedure was used (Table 3). The comparison for the Block Design subtest approached significance, while that for the Digit Symbol subtest was not significant. Differences between the group means were in the expected direction for all of the measures, with patients in the left hemisphere group performing worse on verbal tests and patients in the right hemisphere group exhibiting lower scores on the Facial Recognition test and the Block Design subtest. The group means for these measures are presented in Table 4.

Discussion

This study provides evidence for declines in several cognitive domains in patients with intracerebral glioma, including reductions in verbal intellectual functioning, visual-spatial skills, language, and verbal learning, Our estimate of the severity of these impairments in the brain tumor population at large is conservative because subjects with bilateral or subcortical lesions were excluded. In addition, all data were obtained from a clinical service where older patients and those with more serious disabilities were often administered less demanding tests. These individuals were not included in the present investigation and, again, our findings probably underestimate the severity of cognitive impairments typically associated with intracranial glioma. Despite these biases in subject selection, we documented a level of functioning that was often below expectation for our sample of relatively well-educated tumor patients. Their performance on the neuropsychological test battery was not related to tumor histopathology but was associated with lesion lateralization and with the side effects of radiation and chemotherapy.

We noted that several neuropsychological instruments were sensitive to lesion lateralization. Pa-

Table 2. Univariate tests for therapy

Cognitive measure	N	Univariate F	df	Unadjusted probability
Verbal IQ	207	1.15	2/204	0.3176
Block Design	236	4.65	2/233	0.0104[c]
Digit Symbol	216	14.27	2/213	0.0001[d]
CLTR[a]	153	2.43	2/150	0.0911
Token Test	228	1.25	2/225	0.2898
Visual Naming	230	1.18	2/227	0.3106
COWA[b]	236	3.93	2/233	0.0210
Facial Recognition	194	2.11	2/191	0.1235

[a] Consistent Long Term Retrieval

[b] Controlled Oral Word Association Test

[c] Approaches significance at the 0.10 level when the Bonferroni procedure is used.

[d] Significant at the 0.001 level when the Bonferroni procedure is used.

Table 3. Univariate tests for lateralization

Cognitive measure	N	Univariate F	df	Unadjusted probability
Verbal IQ	207	16.71	1/205	0.0001[e]
Block Design	236	6.88	1/234	0.0093[c]
Digit Symbol	216	3.18	1/214	0.0761
CLTR[a]	153	7.79	1/151	0.0059[d]
Token Test	228	23.26	1/226	0.0001[e]
Visual Naming	230	17.64	1/228	0.0001[e]
COWA[b]	236	26.76	1/234	0.0001[e]
Facial Recognition	194	10.23	1/192	0.0016[d]

[a] Consistent Long Term Retrieval
[b] Controlled Oral Word Association Test
[c] Approaches significance at the 0.10 level when the Bonferroni procedure is used
[d] Significant at the 0.05 level when the Bonferroni procedure is used
[e] Significant at the 0.001 level when the Bonferroni procedure is used.

tients with left hemisphere tumors had lower scores on measures of language, verbal learning, and verbal intelligence. Patients with right hemisphere lesions had greater difficulty with visual-perceptual skills. These results are consistent with those of many studies that have documented similar laterality effects in other focal neurological disorders, such as cerebrovascular accident [24]. However, previous findings in studies of neoplasms have been mixed and have not always supported a relationship between lesion site and type of cognitive impairment. The current study indicated such an association and, in this respect, our results are consistent with the earlier findings of Hom and Reitan [7].

Interestingly, our results failed to replicate Hom and Reitan's observation that cognitive function was worse in patients with fast growing, highly malignant neoplasms than in patients with less aggressive tumors [7]. Failure to address a significant age difference may have biased comparisons between their high and low malignancy groups. In addition, differences in test and subject selection may have contributed to discrepant findings between their study and the current investigation. For example, Hom and Reitan reported that specific measures

Table 4. Mean scores by lateralization

Variable	Left hemisphere		Right hemisphere	
	M	SD	M	SD
Verbal IQ	90.15	13.4	97.74	13.3
Block Design	8.91	2.6	7.96	3.0
Digit Symbol	7.59	2.8	8.29	2.9
CLTR[a]	24.72	15.8	31.35	14.4
Token Test	29.48	37.7	48.62	14.6
Visual Naming	36.66	24.8	47.80	11.3
COWA[b]	38.05	12.0	45.57	9.7
Facial Recognition	50.13	10.2	41.88	23.7

Note: With the exception of measures from the Wechsler Adult Intelligence Scale – Revised (Verbal IQ, Block Design, Digit Symbol), values in this table are T scores with a mean of 50 and standard deviation of 10. Block Design and Digit Symbol are reported as age-corrected scaled scores.
[a] Consistent Long Term Retrieval
[b] Controlled Oral Word Association Test.

from the HRNB were most sensitive to tumor histopathology. None of these instruments were included in the present investigation. However, a previous study showed that performance on a sensitive measure from the HRNB, the Category Test, was not related to malignancy when patient age and level of education were statistically controlled [25]. This finding suggests that Hom and Reitan's results for tumor histopathology might have differed if demographic variables had been taken into consideration.

It is also possible that histopathology is related to cognitive function before surgical intervention but not afterwards. Several earlier studies found greater impairment among patients with highly malignant tumors and most subjects in this early research had not received surgery [2, 3]. In addition, a recent neuropsychological study examined preoperative cognitive function and found that patients with high-grade neoplasms did more poorly than those with low-grade tumors [6]. Other studies, including the current investigation, have failed to find such a relationship in patients who underwent a partial or total resection [25]. These results seem to indicate that the differences on cognitive tests between patients with high and low grade tumors are eliminated, or at least reduced, following surgical intervention.

Chemotherapy and radiation therapy are common treatment modalities and, in the present investigation, their use was associated with some decline in neuropsychological test performance. In particular, scores on the Digit Symbol subtest were significantly lower for patients who had received radiation therapy or combination therapy. Performance on the Digit Symbol subtest was not related to lesion lateralization, however, and lower scores following adjunctive therapy were probably secondary to diffuse cerebral dysfunction associated with treatment side effects. Additionally, there were nonsignificant trends toward lower scores on the Block Design subtest following combination therapy or with right hemisphere lesions. These findings suggest that the Block Design subtest may be sensitive to both focal right hemisphere dysfunction and diffuse pathology secondary to treatment. Measures of more specific cognitive abilities, such as tests of basic language skills and visual perception, were not affected by the use of adjunctive therapy but were related to lesion lateralization. In the present study, these instruments were most sensitive to focal brain dysfunction produced by the tumor and by surgery.

The ability to discriminate between toxic effects of therapy and symptoms associated with the focal lesion may have practical applications. Chemotherapy and radiation therapy have been shown to extend survival time for many patients with intracerebral glioma, but these treatments are often neurotoxic and their long-term side effects may adversely affect quality of life [26]. In some cases, radiation injury may produce a dementia or contribute directly to the death of the patient [27]. The use of cognitive tests to distinguish between neurotoxic effects of treatment and focal effects of the lesion, including those associated with tumor recurrence, may permit the early identification of patients with severe reactions to therapy. This information may indicate a need to modify the treatment plan to allow optimization of both the length and quality of a patient's life.

The present investigation provides some preliminary data about cognitive impairments associated with brain tumors and their treatment, but this study also has some limitations which should be corrected with future research. Many of these limitations are associated with the use of retrospective data from a clinical database, such as the poor availability of specific information about surgical resections and treatment protocols, a lack of quantitative brain imaging data, and incomplete neuropsychological data because some patients were not administered all of the tests. Prospective studies can address many of these issues and several such investigations are currently in progress. However, gliomas are not as common as many other forms of neuropathology (e.g., head trauma, cerebrovascular accident) and it is difficult to obtain large, homogeneous samples of brain tumor patients for research. Information from the current investigation, which is based on a large clinical sample, can complement the data obtained from smaller prospective studies.

Research is also needed to provide additional information about measures which are sensitive to

the side effects of radiation therapy and chemotherapy. If toxic effects of treatment are associated with diffuse cerebral dysfunction, as suggested by prior studies [13], then measures that are sensitive to diffuse pathology in other disorders (e.g., closed head injury, HIV infection) may make good additions to a brain tumor test battery. Tests of choice reaction time and information processing speed may be especially effective for identifying cases of treatment neurotoxicity. These instruments are sensitive to the diffuse pathology associated with other forms of neuropathology, they can detect mild cognitive deficits, and some may be useful in identifying patients who are ready to resume employment or driving [28, 29].

The current study provides some preliminary information about the cognitive deficits associated with glioma, their severity, and the relationship between neuropsychological function and tumor and therapy variables. Such information may be useful for developing test batteries that are sensitive to treatment side effects, as well as planning future research and rehabilitation programs [30].

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